



CLINICAL REPORT

Attention-Deficit/Hyperactivity Disorder and Substance Abuse

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KEY WORDS

ADHD, attention-deficit/hyperactivity disorder, nonstimulant medication, safe prescribing, stimulant medication, substance abuse

ABBREVIATIONS

AAP—American Academy of Pediatrics

ADHD—attention-deficit/hyperactivity disorder

DSM-5—*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*

OR—odds ratio

SUD—substance use disorder

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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abstract

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Attention-deficit/hyperactivity disorder (ADHD) and substance use disorders are inextricably intertwined. Children with ADHD are more likely than peers to develop substance use disorders. Treatment with stimulants may reduce the risk of substance use disorders, but stimulants are a class of medication with significant abuse and diversion potential. The objectives of this clinical report were to present practical strategies for reducing the risk of substance use disorders in patients with ADHD and suggestions for safe stimulant prescribing. *Pediatrics* 2014;134:e293–e301

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood and occurs in approximately 8% of children and youth.^{1,2} It is characterized by deficits in attention in addition to hyperactivity and impulsivity that cause functional impairment in at least 2 settings.³ ADHD is considered a chronic condition.⁴ Stimulant medication is recommended as first-line therapy for school-aged children with ADHD, with implementation of behavioral therapy also recommended. Children with ADHD are at high risk of having co-occurring mental health and behavioral problems, including substance use disorders (SUDs).^{5,6} It is not clear whether stimulant treatment reduces the risk of SUDs in adolescents with ADHD. Some epidemiologic studies have found an inverse association between stimulant treatment and SUDs,^{7,8} although this association was not found in a study that examined the relationship between ADHD, stimulant medication, and conduct disorder.^{9,10} Stimulant medication can also have significant potential for misuse,¹¹ abuse, and diversion^{12,13} (ie, giving away, trading, or selling of prescription medication), which complicates care. Although the potential for misuse and diversion of stimulants has been studied,^{11,12} there is a paucity of recent research on the abuse potential of stimulants among children and adolescents. The objectives of the present clinical report were to review the literature and provide practical suggestions for optimizing ADHD care while minimizing misuse, abuse, and diversion of stimulant medication.

EPIDEMIOLOGY OF SUDS AMONG INDIVIDUALS WITH ADHD

Children and adolescents with ADHD are more likely to misuse alcohol, tobacco, and other illicit substances compared with children without ADHD.^{14,15} In a 2011 meta-analytic review of the prospective association of childhood ADHD and substance use, Lee et al¹⁴ included 27 longitudinal studies that followed up children with and without ADHD into adolescence or adulthood. The following demographic/methodologic factors did not significantly moderate the associations between childhood ADHD and substance outcomes: gender, age, race, publication year, sample source, version of the *Diagnostic and Statistical Manual of Mental Disorders* used to diagnose ADHD, family history of SUD, cognitive impairment, executive dysfunction, and family environment.¹⁶ Lee et al reported that, compared with control subjects without ADHD, children with ADHD were:

- twice as likely to have a lifetime history of nicotine use (odds ratio [OR]: 2.08, $P < .001$);
- nearly 3 times more likely to report nicotine dependence in adolescence/adulthood (OR: 2.82, $P < .001$);
- almost 2 times more likely to meet diagnostic criteria for alcohol abuse or dependence (OR: 1.74, $P < .001$);
- approximately 1.5 times more likely to meet criteria for marijuana use disorder (OR: 1.58, $P = .003$);
- twice as likely to develop cocaine abuse or dependence (OR: 2.05, $P < .001$); and
- more than 2.5 times more likely to develop an SUD overall.

ADHD is associated with an earlier age at onset of substance use and a higher likelihood of use of a variety of substances.^{17–19} Brook et al²⁰ reported that the diagnosis of ADHD poses an increased risk of SUD into adulthood;

meeting criteria for a diagnosis of ADHD in adolescence is associated with developing SUDs in a subject's 20s and 30s. Among individuals with ADHD, the number of inattention and hyperactivity/impulsivity symptoms exhibited is positively correlated with risk of substance use.²¹ Debate exists regarding whether the inattentive versus hyperactive/impulsive subtypes of ADHD confer different risk.^{22–26}

EXPLORING THE BIOLOGICAL AND ENVIRONMENTAL BASIS OF THE RELATIONSHIP BETWEEN ADHD AND SUD

To date, the mechanisms underlying the association between ADHD and SUDs are not completely understood, although several theories have been proposed. Impulsivity is associated with an increased risk of substance use,²⁷ a prerequisite for developing an SUD. It is also possible that impulsivity and poor judgment associated with ADHD contribute to the development of SUDs.²⁸ However, executive functioning deficits and increased substance use seem to be only one piece of the puzzle.²⁹ In addition to difficulty with executive functioning and poor judgment, which may lead to trying substances, individuals with ADHD may also be biologically more vulnerable to developing addiction than their peers without ADHD.

Dopamine transmission is central to current models of both ADHD and SUDs.^{30–32} Compared with unaffected control subjects, individuals with ADHD have greater dopamine transporter density, which may result in rapid clearance and low levels of synaptic dopamine.³³ Drugs of abuse, including cocaine, amphetamine, methamphetamine, Ecstasy, nicotine, alcohol, opiates, and marijuana, all increase synaptic dopamine concentrations, most notably in the brain's reward center, the nucleus accumbens.³⁴

Stimulant medications manage ADHD symptoms by increasing synaptic dopamine concentrations in the striatum (which includes the nucleus accumbens) via presynaptic transporters.³⁵ Theoretically, some individuals with ADHD may use substances to increase synaptic dopamine concentrations as a form of self-medication.³⁶ Another theory proposes a common genetic factor underlying both ADHD and risk of SUDs, although more studies are needed to further evaluate this association.^{37,38}

Children and adolescents with ADHD have higher rates of grade retention and school dropout than those without ADHD.^{39,40} These academic failures may increase an individual's likelihood to use drugs as a means to escape anxiety about school.⁴¹ Academic failures may also cause changes in peer groups, placing the individual with ADHD in social settings with others who have experienced school problems and are at a higher risk of alcohol and drug use.^{42,43}

TREATING ADHD AND CO-OCCURRING MENTAL HEALTH DISORDERS TO REDUCE THE RISK OF SUDS

Treatment of ADHD May Reduce the Risk of SUDs

Treatment of ADHD symptoms with stimulant medication may reduce the risk of developing SUDs.^{7,44} Biederman et al⁴⁵ determined that pharmacotherapy was associated with an 85% reduction in risk of SUDs in youth with ADHD. Timing of treatment matters: children with ADHD who are treated with stimulant medication at a younger age are less likely to use substances than those who have delayed onset of treatment.⁴⁶ Behavioral therapy may also confer some protection against substance use. Findings from the Multimodal Treatment Study of Children with ADHD revealed that

behavioral interventions afforded protection from SUDs at 24 months' post-intervention but not at 36 months.⁴⁷ The optimal age at which to begin treatment of ADHD to decrease the risk of substance use has not been established. The American Academy of Pediatrics (AAP), in its clinical practice guidelines for ADHD,⁴ recommends treating ADHD symptoms in children 6 years and older by using both behavioral interventions and medications approved by the US Food and Drug Administration. The AAP recommends that ADHD symptoms in children as young as 4 years be treated with behavioral interventions and possibly medications. In this context, treatment of ADHD symptoms is recommended as soon as the diagnosis of ADHD is made. Symptoms of ADHD often persist into adulthood,^{48,49} although optimal duration of medication treatment has not been established. Maintaining children on medication while symptoms persist and monitoring for adverse effects seems to be a reasonable approach.

As noted in the AAP clinical practice guidelines for ADHD,⁴ at any point at which a clinician believes that he or she is not adequately trained or is uncertain about making a diagnosis or continuing with treatment, a referral to a pediatric or mental health subspecialist should be made. If a diagnosis of ADHD or other condition is made by a subspecialist, the primary care clinician should develop a management strategy with the subspecialist which ensures that the child will continue to receive appropriate care consistent with a medical home model wherein the primary care clinician partners with parents so that both health and mental health needs are integrated.

Treating Co-occurring Mental Health Disorders

Co-occurring mental health conditions are common in individuals with ADHD and are associated with increased SUD

risk. Brook et al²⁰ determined that conduct disorder mediated the association of ADHD and SUDs. Other studies have revealed that, even after controlling for conduct disorder, ADHD symptoms are associated with increased risk of both substance use and development of SUDs.^{18,25} Comorbid conditions, including depression, anxiety, and low self-esteem, have each been noted to confer increased risk of substance use in individuals with ADHD.^{5,17,25,50,51} These findings suggest that diagnosing and treating co-occurring conditions in individuals with ADHD may help to reduce the risk of developing SUDs.

STIMULANT MEDICATIONS

Stimulant medications are highly effective for children and adolescents in reducing the core symptoms of ADHD.⁵² The most commonly used preparations of stimulant medication are methylphenidate and amphetamine. Atomoxetine, a selective norepinephrine reuptake inhibitor, and long-acting guanfacine and clonidine, which are selective α_2 -adrenergic agonists, are also recommended for the management of some ADHD symptoms.⁴ However, the effect sizes (meaning likelihood of reducing ADHD symptoms compared with placebo) are lower for atomoxetine and long-acting guanfacine and clonidine than they are for the stimulant medications.

Stimulant medications are both more effective at treating ADHD symptoms⁵³ and much more commonly misused than nonstimulant medications. Pediatricians are thus in a position to prescribe a medication that can reduce both ADHD symptoms and the risk of developing an SUD and simultaneously pose a risk for abuse and diversion. An understanding of the factors associated with misuse, abuse, and diversion of stimulant medication may help to guide safe use. Table 1 lists the most commonly

used medications for ADHD and their suspected relative abuse potential.

The terms "misuse," "diversion," and "abuse" are all associated with improper use of medication, but they are different phenomena with different definitions. The term misuse includes the use of medications not prescribed to the individual and using medications in ways other than prescribed. Examples of misuse include taking larger or more frequent doses than prescribed or using someone else's medication to enhance performance.¹³ The most common reasons reported for stimulant misuse are to concentrate, study, and improve grades; "to party" and "get high"; and to experiment.^{54–57} Most individuals who misuse stimulant medications do so via oral administration, with intranasal insufflation ("snorting") less common.^{43,46} Adolescents who report snorting medications or using stimulants to "get high" may be at highest risk of stimulant abuse and dependence.⁵⁸ The term diversion means the transfer of medication from the person to whom it is prescribed to a person for whom it is not prescribed.¹³ The term substance abuse was used in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, to refer to use associated with problems or risk that interfere with functioning. The term addiction refers to loss of control or compulsive use of a substance. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), diagnostic terms were changed to SUD, mild/moderate/severe, depending on the number of positive criteria.³ Even though they are not formal diagnoses, the terms substance abuse and addiction will likely remain in the lexicon and retain their meaning for some time, particularly in reference to prescription medications.

TABLE 1 List of Most Commonly Used Medications for ADHD With Suspected Relative Abuse Potential

Stimulant Status	Medication Type	US Trade Name ^a	Suspected Relative Abuse Potential ^b
Stimulants			
Short-acting/immediate release	Methylphenidate	Ritalin ^a	High
		Methylin ^a	High
	Dexamethylphenidate	Focalin ^a	High
		Amphetamine-dextroamphetamine	Adderall ^a
	Dextroamphetamine	Dexedrine	High
		DextroStat ^a	High
ProCentra		High	
LA/ER	Methylphenidate	Metadate CD	Medium
		Metadate ER ^a	Medium
		Ritalin LA ^a	Medium
		Ritalin SR ^a	Medium
		Methylin ER	Medium
		Daytrana patch	Low
		Concerta ^a	Low
	Dexamethylphenidate	Quillivant XR	Low
		Focalin XR	Low
	Dextroamphetamine	Dexedrine Spansule ^a	Medium
	Amphetamine-dextroamphetamine	Adderall XR ^a	Medium
	Lisdexamfetamine	Vyvanse	Low
	Nonstimulants		
α_2 -adrenergic agonists	Guanfacine	Intuniv	Low
		Clonidine	Low
Selective norepinephrine reuptake inhibitor	Atomoxetine	Strattera	Low

CR, controlled release; ER, extended release; LA, long acting; XR, extended release; SR, sustained release.

^a Indicates that generic formulation is available.

^b Relative abuse potential is suspected based on length of action and formulation of medication.

Misuse of Stimulant Medications

Misuse and diversion of stimulant medications are more widespread problems than abuse or addiction.⁵⁹ Wilens et al⁵⁴ conducted a systematic review of the literature examining misuse and diversion of prescription ADHD medications. Of the 21 studies reviewed, rates of past-year non-prescribed stimulant use ranged from 5% to 9% in grade school and high school children and from 5% to 35% in college-aged individuals. In a large public university in the mid-Atlantic region, Arria et al⁵⁵ found that 18% of students who were not prescribed stimulants engaged in nonmedical stimulant use, more than one-quarter (26.7%) of students with diagnosed ADHD reported having used more medications than prescribed, and 15.6% reported using someone else's

prescription stimulants in their lifetime. Nonmedical use of prescription stimulants was associated with previous use of illicit substances as well as alcohol and marijuana dependence.

Diversion of Stimulant Medications

Diversion of stimulant medication is common. Between 16% and 23% of school-aged children reported that they have been approached to sell, give, or trade their prescription stimulant medication.^{60,61} Boys are more likely to divert their stimulant medications than girls.⁶² The most common source of diverted medications is friends and family members.⁶³ More than one-quarter of university students reported that diverted stimulant medications are easy or somewhat easy to obtain.⁵⁶ Individuals with ADHD who have co-occurring SUDs and/or conduct

disorders are more likely to both misuse and divert their stimulant medication,⁶⁴ as are white individuals, members of fraternities and sororities, and students with lower grade-point averages.^{54,65}

Abuse of Stimulant Medications

Methylphenidate and amphetamine both have known abuse potential, although there is little evidence that these drugs are widely abused by the patients to whom they are prescribed,⁵⁹ and evidence for abuse potential among children and adolescents is limited. "Subjective effect" (ie, how much a person likes a drug, achieves euphoria, experiences reinforcement with use) is an important factor considered in determining abuse potential of a substance. Among individuals without ADHD, both methylphenidate and amphetamine produce significant subjective effects; amphetamine is nearly twice as potent as methylphenidate at equivalent doses.⁶⁶ Research performed in the 1970s revealed that stimulants do not reliably produce these subjective effects in individuals with ADHD.⁶⁷ Fredericks and Kollins⁶⁸ found that individuals with ADHD displayed a higher preference for methylphenidate compared with placebo, although other measures of abuse potential, specifically participant-rated effects of methylphenidate on mood, were not elevated. Thus, the preference for methylphenidate may reflect its therapeutic efficacy rather than abuse potential. Most of the studies evaluating abuse potential of stimulant medications used short-acting preparations, and there is evidence that sustained-release and longer acting preparations have decreased abuse potential.^{59,69} Indeed, short-acting medications are more likely to be misused or abused, and amphetamine preparations are misused and abused more frequently than methylphenidate preparations.^{53,70,71}

SAFE STIMULANT-PRESCRIBING PRACTICES

In light of the high risk of SUDs among individuals with ADHD, pediatricians should seek to accurately diagnose ADHD and treat symptoms appropriately. Several precautions may help to reduce stimulant misuse, abuse, and diversion.

Before Prescribing, Confirm a Diagnosis of ADHD

Inattention is multifactorial. Many children or adolescents who are depressed, anxious, neglected, or having academic difficulty because of a learning disorder may present as inattentive. ADHD is a primary disorder of attention. According to the diagnostic criteria for ADHD in the DSM-5,³ ADHD symptoms must be present during childhood; thus, particular caution is warranted before making a new diagnosis of ADHD, especially in an adolescent. Although it is possible that symptoms in childhood were unnoticed, adolescents sometimes attempt to get a stimulant prescription by feigning symptoms of ADHD.⁷² The diagnosis of ADHD is made clinically in an individual who fulfills the criteria for ADHD listed in the DSM-5.³ Standardized tools, such as parent- and teacher-completed ADHD rating scales, assist in making a diagnosis and should be used in the assessment.⁷³ A thorough history, review of medical and school records, and a collateral parent interview may all help confirm a correct diagnosis. The criteria used for diagnosing ADHD and any history or evaluations that were made to rule out other conditions that might be confused with ADHD (eg, sleep disturbances, other learning disabilities, thyroid dysfunction) should be recorded in the patient's medical record. The AAP's Clinical Practice Guideline for ADHD provides specific guidance about diagnosis and management.⁴

Screen Older Children and Adolescents for Use of Alcohol, Marijuana, and Other Drugs

The AAP recommends screening, brief intervention, and referral to treatment as part of routine health care for older children and adolescents.⁷⁴ This recommendation is particularly important for adolescents with ADHD, who are more likely to use substances and to develop an SUD than their peers. Adolescents with ADHD who use alcohol, marijuana, or other substances are also more likely to divert stimulant medication and thus require increased attention and monitoring by their prescriber.

The AAP policy statement titled "Substance Use: Screening, Brief Intervention, and Referral to Treatment for Pediatricians"⁷⁴ provides a complete review of recommended screening tools and brief interventions for adolescent substance use. The AAP currently recommends the 3 "opening questions" associated with the CRAFFT tool (see the following text) to detect past-year substance use. Although currently an active area of National Institutes of Health–funded research,^{75,76} these questions have not been validated to date, and it is not known whether the "other drugs" question is sensitive enough for identifying misuse or abuse of prescription medications. An additional question (eg, "Have you ever used someone else's prescribed medication?") may be warranted to identify misuse, particularly before prescribing a stimulant medication for the first time.

"Opening questions" to identify past-year substance use:

In the past year, have you:

1. Had a drink with alcohol in it?
2. Used marijuana?
3. Used any other substance to get high?

Provide Anticipatory Guidance

Anticipatory guidance regarding proper use of stimulant medications should be part of every patient encounter in which medications for ADHD are discussed. Table 2 lists points that should be included in this discussion. The pediatrician should discuss that medications should only be taken as prescribed by the physician, even with very young children, in a developmentally appropriate manner. As children enter the upper elementary school years, the conversation should evolve to include discussion about the proper use of medication. Children and parents should be aware of the risk for misuse, diversion, and abuse. Children should understand that trading or selling stimulant medication is illegal. Children who live in areas of high-crime rates should have a concrete, realistic safety plan for managing their medication. For children who are 12 years and older, the discussion should also include information about careful transitioning of administration of medication. Although the child should not be pushed to start self-administering medication, having this discussion earlier with the family can alert them that transition of medication management from caregiver to child should be a gradual and carefully monitored one so that when the child is developmentally ready to assume more responsibility of medication management, there is a plan in place to ensure that the transition is safe.

Document Prescription Records

Stimulant medication is a Drug Enforcement Administration Class II controlled substance. Every prescriber must document and monitor the prescribing of stimulant medications. Requests for early refills should be explored and carefully documented to

TABLE 2 Discussion Points for Anticipatory Guidance Regarding Stimulants and Substance Use

Proper administration

At each clinic visit, review with the patient how he or she is taking his or her stimulant medication.

- Only take the amount of medicine prescribed. Do not take extra medication.
- Take your stimulant medication exactly as prescribed. Do not change the dose or timing. Speak to your doctor if you do not think your medication is working as it should or if you are experiencing adverse effects.
- Do not use alcohol, tobacco, marijuana, or other illicit substances. Drug use worsens problems with attention, leads to medication noncompliance, and can interact with stimulant medication.
- If stimulant medication is administered at school, it should be dispensed at school nurse's office or other safe location with adult supervision.

Risk of misuse, diversion, and abuse

For people who do have ADHD, when stimulant medications are taken as prescribed, there is no increased risk of abuse; rather, stimulant medication appears to decrease the risk of developing an SUD.

- Explain that some people who do not have ADHD may take stimulant medications inappropriately.
- Inform patient and parent that children and adolescents may be asked to give away or sell their stimulant medications but should never do so. Parents may role play appropriate responses so that the child will be prepared if asked. Have the patient and parents keep medication in a safe location (either at home or in a locked office at school). Medications should never be carried in a backpack or purse.

Transition of care

Transitioning of administration of stimulant medication from caregiver to child/adolescent should be done incrementally. Parents and patients should be counseled that ADHD generally persists into adulthood.

- To start a transition, the child/adolescent must be able to remember to take medication as prescribed. Signs suggesting readiness should include the ability to name the medication, dose, and timing of administration as well as emerging signs of independence in other areas, such as being home alone, carrying a key, completing homework independently, or participating in care for a pet.
- The caregiver should continue to periodically supervise medication administration and monitor the child's/adolescent's overall school, social, and family functioning. Weekly pill dispensers can allow burgeoning autonomy for the child/adolescent while allowing the caregiver to monitor doses and control the supply.
- If concerns develop regarding medication misuse or diversion or use of other drugs, the parent should resume control of the medication, dispense each dose, and monitor carefully.

detect a pattern of frequent early requests. Similarly, it is important to document communications between multiple providers who share responsibilities for prescribing medications or altering treatment regimens for the same patient.

Prescribing Medications for ADHD in Context of Active SUD

Illicit substance use often results in attention difficulties, hyperactivity, and/or impulsivity, making a new diagnosis of ADHD difficult or impossible to distinguish from symptoms related to ongoing substance use. In these cases, reevaluation after a period of abstinence may be warranted.

Adolescents who have both previously diagnosed ADHD and an active SUD may be difficult to monitor because

symptoms of substance use may be indistinguishable from ADHD symptoms. In general, an active SUD should be treated (usually via referral to a mental health counselor or addiction specialist) before beginning medication to treat ADHD. However, for patients with well-documented ADHD that predates the onset of substance use, it may be reasonable to treat both disorders concurrently. Consultation with a psychiatrist or addiction specialist when managing complex patients is suggested.

When considering which ADHD medication to prescribe to a patient with a co-occurring SUD, a careful risk/benefit assessment must be conducted. If the patient is currently abusing prescription stimulants or there is a clear indication that the patient would sell or divert stimulant

medication, it may be best to start with a long-acting stimulant medication with low risk of misuse or diversion. Long-acting preparations, especially those with an osmotic controlled-release oral delivery system such as Concerta, have lesser likelihood of misuse or diversion.⁷⁷ It is also reasonable to consider use of a non-stimulant preparation,⁷⁸ even though nonstimulant medications are less efficacious than stimulants.⁷⁹ The prodrug formulation of dextroamphetamine, lisdexamfetamine, has a lower abuse potential than other stimulants and thus may be considered.^{80,81} However, physicians should be aware that any psychoactive medication can be misused. As for all patients, it is important to carefully monitor medication adherence.

A special circumstance occurs when a pediatrician prescribes stimulant medications for college students and older patients living away from home. A treatment plan should document how medication will be prescribed and how frequently the patient is expected to return for follow-up visits with the pediatrician. Medication administration by a student health staff member or keeping medications in a small medication safe may reduce diversion or theft. Follow-up visits should include self-report of medication efficacy, adverse effects (appetite, abdominal symptoms, headaches, and sleep disturbance) and screening for medication misuse, abuse, or diversion. The patient's responses should be documented in the medical record. Reports or suggestions of new physical or mental health symptoms require reevaluation.

SUMMARY

ADHD is a common neurobehavioral disorder of childhood, and individuals with ADHD are more likely to misuse alcohol, tobacco, and other illicit

substances compared with children and adolescents without ADHD. Individuals with ADHD and co-occurring mental health conditions, such as disruptive behavior disorders or depression, are at even higher risk of developing SUDs. Appropriate treatment of ADHD symptoms with medication and behavior therapy may reduce the risk of development of SUDs. Primary care providers should seek to identify and treat ADHD to prevent the development of SUDs. However, the recommended first-line medication therapy for ADHD is stimulant medications, which themselves pose a risk of misuse, diversion, and abuse. Therefore, an important part of ADHD treatment and stimulant medication management

includes screening for SUDs and providing anticipatory guidance around the appropriate and safe use of stimulant medications. Individuals with co-occurring ADHD and active SUDs require a careful, individual risk/benefit assessment regarding the safety of prescribing a stimulant medication. Longer acting preparations of stimulant medication, the prodrug formulation of dextroamphetamine, and non-stimulant medications for ADHD all have lower abuse potential than short-acting preparations of stimulant medication and, thus, their use should be strongly considered if there is a high risk of misuse, diversion, or abuse of stimulant medications.

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